## REMARKS

**Claims of Priority under 35 U.S.C. §120**

1. According to the Office, applicants are not entitled to the claim priority to US Patent No. 7,084,121 with priority back to US Patent No. 6,713,452, for the following reasons.

> Applicant's claim for the benefit of a prior-filed and co-pending application No. 10806523 filed 3/23/04, which is a CON of 09873777 filed 6/04/01 (now US Pat. No. 6713452), under 35 U.S.C. 120 is acknowledged.
>
> However, 10806523 does not disclose instant method of treating peripheral pain using a mixture of conjugate comprising the first and second oligomers covalently linked to $Lys^{11}$ and $Lys^{18}$ of salmon calcitonin. Thus, claims 1-3 are not granted priority to 6/04/01 the filing date of 09/342364 which is parent application of 10806523. Thus, instant invention is entitled to the filed date 6/24/03 of 60482130, which has full support for claims 1-3.

Applicants disagree because US Patent No. 7,084,121 does provide support for the presently claimed invention.

The Office has numerously reminded applicants in the October 6, 2009 Office Action that Paget's disease is a bone disorder associated with intense pain. Thus, when the text of US Patent No. 7,084,121 (Column 1) discusses Paget's disease and pain, such as below, the Office should recognize that the discussion of Paget's disease and pain is included in the patent specification.

Paget's disease of bone is a metabolic bone disorder of unknown origin which normally affects older people. The disease causes an increased and irregular formation of bone as the bone cells, which are responsible for dissolving the body's old bone and replacing it with new, become out of control. Over a period of time the deformed new bone becomes larger, weaker and has more blood vessels than normal bone. Unlike normal bone, the structure is irregular and consequently weaker, which makes it prone to fracture even after a minor injury.

In its mildest form the disease has no symptoms. In more severe cases the pain can be intense. The relentless progression of the disease may cause bones to bow, the skull may increase in size and the spinal column may curve. As the bones enlarge they may cause pressure on nearby nerves which can result in muscle weakness. In the case of severe skull enlargement this pressure can result in deafness, disturbed vision, dizziness and tinnitus.

Further in column 47 of US Patent No. 7,084,121, there is a discussion of methods of treatment of Paget's disease such as shown below:

Methods of treating a bone disorder in a subject in need of such treatment by administering an effective amount of such pharmaceutical compositions are also provided. The bone disorder is preferably characterized by excessive osteoclastic bone resorption and/or hypercalcemic serum effects. Bone disorders that may be treated and/or prevented by methods of the present invention include, but are not limited to, osteoporosis, Paget's disease, and hypercalcemia.

According to the Office, U.S. Patent No. 7,084,121, which is a continuation of US Patent No. 6,713,452 (thus the exact same specification), describes the following:

Claims 11-12 of 121' disclose a method of treating osteoporosis Paget's disease (a bone disorder associated with intense pain in some stage thereof, see col. 1, lines 47-59) comprising administering PEGylated calcitonin wherein the calcitonin peptide is coupled to at least one PEG moiety encompassing "two PEG moieties". Since the calcitonin peptide contains two internal lysine residues $Lys^{11}$ or $Lys^{18}$, claims 12-13 are obvious variation of instant claim 1.

Claim 6 of 121' discloses that calcitonin is covalently coupled to the polyethylene glycol moiety by a hydrolyzable bond, a non-hydrolyzable bond or both; and thus, claims 11-12 together with claim 6 are obvious variation of instant claim 2.

Thus the Office recognizes that US Patent No. 7,084,121 teaches the treatment of pain with a conjugate comprising two PEG moieties covalently coupled to the calcitonin.

According to 35 U.S.C. §120, applicants may claim benefit to an earlier application if the invention is described to meet the requirements of 112, as shown below:

**35 U.S.C. 120 Benefit of earlier filing date in the United States.**

An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

It is well settled in the law that for a prior application to meet the "written description" requirement with respect to later-filed claims, the prior application need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the earlier date the applicant had invented what is now claimed. *Vas-Cath Inc. v. Mahurkar,* 19, USPQ 2d 1111, (Fed. Cir. 1991); see *In re Wertheim*, 191 USPQ 90 (CCPA 1976) (" [L]ack of literal support . . . is not enough . . . to support a rejection under Section 112.") The test is whether the

disclosure of the application relied upon reasonably conveys to a person skilled in the art that the inventor had possession of the claimed subject matter at the time of the earlier filing date. *Ralston Purina Co. v. Far-Mar-Co, Inc* ., 227 USPQ 177 (Fed. Cir. 1985). Clearly, US Patent No. 7,084,121 meets this criteria because of the Office has discussed all the present claim limitations that can be found in the specification of US Patent No. 7,084,121, as shown above. Further, it is well settled in the law that a later explicit description of an inherent property, such as treating pain, does not deprive the product or method of the benefit of the filing date of an earlier application. See *Therma-Tru Corp v Peachtree Door Inc*., 33 USPQ2d 1274 (Fed Cir 1994). Still further, the specification of US Patent No. 7,084,121 meets the enablement requirements because the specification describes synthesis and administration of the calcitonin conjugates of the present invention. Thus a skilled artisan can easily recreate the present invention without undue experimentation.

Although the Office never mentioned the requirements of section 112, first paragraph relating to priority claims under 35 U.S,C. §120, applicants insist that the specification of US Patent No. 7,084,121 meets such requirements. As such, applicants request reconsideration and a finding that all claims recited in the present application are entitled to the effective filing date of June 4, 2001.

2. Applicants have amended the specification to include a claim of priority to co-pending U.S. Application No.10/235,284 filed on September 5, 2002, and a priority date of September 7, 2001, with a title of "PHARMACEUTICAL COMPOSTITIONS OF CALCITONIN DRUG-OLIGOMER CONJUGATES AND METHODS OF TREATING DISEASES THEREWITH" now U.S. Patent No. 6,770,625. Applicants are entitled to claim priority to this application because there is at least one common inventor and the specification provides ample support for the composition and methods of the presently claimed invention. Notably, the Office pointed to this full support by citing and expressly pointing out the claimed limitations of the presently claimed invention, as shown below:

Claims 1-3 are rejected under 35 U.S.C. 102(e) as anticipated by Soltero et al. (US 6770625 B2).

In patent claim 62, Soltero et al. teach a method of treating a bone disorder such as "Paget's disease" which has intense pain symptom (see "*Discussion of art*" [2]) comprising administering to a subject in need a pharmaceutical composition comprising "calcitonin (CT)-drug-oligomer conjugate"; wherein CT is salmon calcitonin (patent claim 38), and wherein the "oligomer" preferably is "polyethylene glycol" (PEG) (see col. 24, lines 27, 35 and 36) linked to $Lys^{11}$ and $Lys^{18}$ residues of calcitonin (patent claim 38). Thus, Soltero et al. inherently teach the method of instant claim 1.

Soltero et al. teach the structure: "Salmon calcitonin-[CO-$(CH_2)_7$-$(OC_2H_4O)_7CH_3$]$_2$" (see col. 31, lines 3-8) wherein "-$(OC_2H_4O)_7$" is PEG moiety subunits (see col. 25, lines 7-16), "CO-$(CH_2)_7$-" is a lipophilic moiety that preferably is a fatty acid moiety (see col. 25, lines 37-40), and wherein "2" in outside parentheses "[ ]" indicates two residues of CT peptide, i.e., $Lys^{11}$ and $Lys^{18}$, are conjugated to the PEG moieties. This meets the structural limitation of the "conjugate" of claim 3; and thus, Soltero et al. teach the method of instant claim 3.

Soltero et al. teach that a (one) hydrolysable bond between drug peptide and the "oligomer" (see col. 33, lines 47-50). In accordance with the claim 38 disclosure that PEG is coupled to the "oligomer" (i.e., calcitonin) via $Lys^{11}$ and $Lys^{18}$ residues of calcitonin, thus, one of these two ε-lysine amino groups is conjugated to the PEG through said "hydrolysable bond" while the other remains non-hydrolysable. This meets the structure of claim 2 "conjugate". Therefore, Soltero et al. inherently teach the method of instant claim 2.

As previously stated, the test to meet the 112 description requirement is that the disclosure of the previous application relied upon reasonably conveys to a person skilled in the art that the inventor had possession of the claimed subject matter at the time of the earlier filing date. Clearly, US Patent No. 6,770,625 meets this criteria because of the Office has discussed all the present claim limitations that can be found in the specification of US Patent No. 6,770,625, as shown above. Further, it is well settled in the law that a later explicit description of an inherent property, such as treating pain, does not deprive the product or method of the benefit of the filing date of an earlier application.

Thus, the present application is entitled to the effective filing date of September 5, 2002. Applicants have included herewith a petition under 37 CFR 1.78((a)(3) to the Commissioner for Patents, requesting the acceptance of an unintentionally delayed claim under 35 USC 120 (Appendix A). Further, applicants have included a statement that the entire delay between the 371 filing date of December 22, 2005 of the present application and the date of filing this petition of January 6, 2010 was unintentional. As such, applicants respectfully request that all claims recited in the present application be given the effective filing date of September 5, 2002.

**Objection of Claims**

Applicants have amended claim 1 to remove the text "function" and replace with "group" according to the suggestion of the Office, thereby obviating this objection.

**Rejection of Claims and Traversal Thereof**

In the October 6, 2009 Office Action,

Claims 1 and 3 were rejected under 35, U.S.C.§112, second paragraph;

Claims 1-3 were rejected under 35 U.S.C.§102(e) as being anticipated by Soltero et al, (US Patent No. 6,770,625, hereinafter Soltero;

Claim 1was rejected under 35 U.S.C103(a) as being obvious over Lee et al (US Patent No. 6,506,730, hereinafter Lee);

Claim 1 was rejected under 35 U.S.C.§103(a) as being obvious over Russo (US Patent No. 5,976,788, hereinafter Russo) in view of Komarova et al. (*Calcif. Tissue Int.*73, 265-273 (published on line 6/6/2003), hereinafter Komarova) and Lee;

Claim 2 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and in view of Katre, et al (US Patent No. 4,917,888, hereinafter Katre '888) and Lee;

Claim 3 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and Katre, Crotts et al. (US 2003/0017203, hereinafter Crotts) and Lee;

Claims 1-2 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 11 and 12 of US Patent No. 7,084,121; and

Claims 1-3 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38 and 62 of US Patent No. 6,770,625.

Applicants traverse these rejections and insist that none of the cited references alone or in combination defeats the patentability of the presently claimed invention.

**Rejection under 35 U.S.C.§112, second paragraph**

Claims 1 and 3 were rejected under 35, U.S.C.§112, second paragraph as being indefinite for failing to particularly point and out and distinctly claim the subject matter which applicant regards as the invention. According to the Office, the term "salmon calcitonin" has been expanded to include salmon calcitonin precursor polypeptide or matured polypeptide thereof, and thus, to have the numbering correct for the $Lys^{11}$ and $Lys^{18}$ amino acid residues, the exact amino acid sequence must be included.

Applicants disagree because there is a clear definition of "Calcitonin" in the specification as shown below:

[0110] As used herein, the term "calcitonin" means chicken calcitonin, eel calcitonin, human calcitonin, porcine calcitonin, rat calcitonin or salmon calcitonin provided by natural, synthetic, or genetically engineered sources.

Notably, applicants have clearly defined the meaning of "calcitonin" in the application, and thus, when the applicants state the meaning of a claim term, the claims are examined with that meaning. See *In re Zletz,* 13 USPQ2d, 1320 (Fed. Cir. 1989).

It should be noted that when rejecting a claim under section 112, second paragraph, it is incumbent on the Office to establish that one of ordinary skill in the art, when reading the claims in light of the specification, would not have been able to ascertain with a reasonable degree of precision and the area set out and circumscribed by the claims. *Ex parte Wu,* 10 USPQ2d 2031, (BPAI 1989). The Office has not met this burden because a skilled artisan would read the claims in light of the specification, wherein the term "calcitonin" is clearly defined and not expanded according to the speculation of the Office.

Applicants request the withdrawal of this rejection under section 112, second paragraph.

**Rejection under 35 U.S.C.§102(e)**

Claims 1-3 were rejected under 35 U.S.C.§102(e) as being anticipated by Soltero with a filing date of September 5, 2002. Notably, applicants have filed herewith a petition under 37 CFR 1.78((a)(3) to the Commissioner for Patents, requesting the acceptance of an unintentionally delayed claim under 35 USC 120 (Appendix A). Thus, this reference is no longer competent prior art and the rejection should be withdrawn.

**Rejections under 35 U.S.C.§ 103(a)**

1. Claim 1 was rejected under 35 U.S.C103(a) as being obvious over Lee. Applicants insist that Lee does not disclose, teach or suggest the presently claimed invention.

Applicants' invention, as set forth in claim 1, describes a method for **orally administrating** to the subject an effective amount of a **substantially monodispersed mixture of conjugates**, wherein the conjugate comprises a first oligomer and a second oligomer **conjugated at the $Lys^{11}$ and $Lys^{18}$ amine functionality of calcitonin.**

According to the Office, Example 4 shows the production of a diconjugate wherein pegylation occurs at $Lys^{11}$ and $Lys^{18}$ of calcitonin. Applicants submit that Example 4 does not teach a diconjugate with a PEG at both $Lys^{11}$ and $Lys^{18}$ functionality but instead Example 4 only teaches monconjugates.

Example 4 refers to placement of PEG moieties at different pHs and this is discussed in the Brief Description of the Figures and shown in Figure 2, as recreated below.

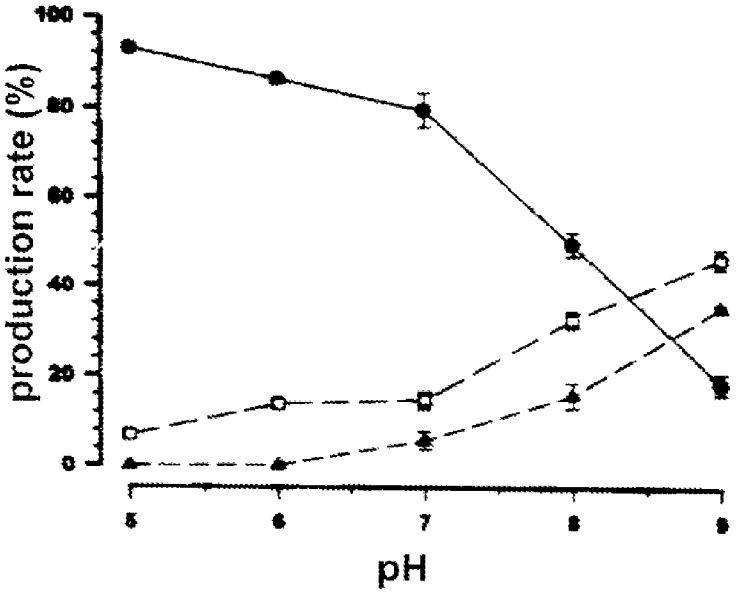
FIG. 2 shows the pH effect on the production of mono-PEG-sCT when PEG is conjugated with N-terminus of calcitonin, $Lys^{18}$ or $Lys^{11}$, where

●; mono-PEG-sCT(N-terminal conjugate),

□; mono-PEG-sCT($Lys^{18}$-conjugate),

▲; mono-PEG-sCT($Lys^{11}$-conjugate).

FIG. 2




It is evident as stated in Example 4 that as the pH increases to 8 or above more monoconjugated calcitonin at the $Lys^{11}$ and $Lys^{18}$ amine functionalities is produced, albeit individually. There is nothing in this example that discusses, teaches or suggests a calcitonin conjugate with a PEG moiety at two lysine amine groups at the same time. Thus, this reference does not teach or suggest each of the recited limitations of the presently claimed invention.

Further, the Lee reference only describes compositions for nasal administration. Thus, the Lee reference does not teach or suggest the presently claimed invention, but instead teaches away from

going in the direction of applicants' claimed invention. Specifically one skilled in the art reading Lee would quickly note that Lee is teaching away from any orally administered compounds.

The Office has stated numerous times that because injection causes pain that there is a need to develop other routes which is exactly what Lee accomplished. However, one reading this Lee reference would quickly note that Lee discourages the use of oral route, and as such, would never consider going in the oral direction just because an injection is painful. Lee immediately discussed the negative side effects of oral administration and instead went in the direction of nasal delivery. For example, at the bottom of column 1, Lee discusses the disadvantages of oral compounds, as recreated below:

> In fact, the nasal mucosa is a direct absorption route through which drugs can circumvent the liver metabolism, which is a great hindrance to the utilization of drugs in the body upon oral administration. Thus, the nasal transmucosal route has an advantage over the oral route in that the body utilization of drugs can be significantly improved.

Further, Lee reiterates the negative side of oral administration at the bottom of column 3 and recreated below:

> As mentioned above, the nasal transmucosal delivery of peptides alone is significantly improved in absorption efficiency compared with the oral administration because the peptides are not subjected to liver metabolism, but poor in the bioavailability of the peptides because they are degraded by endogenous enzymes.

It is well settled in the law that if a cited reference teaches away from going in the direction of applicants' claimed invention then the Office has not established a *prima facie* case of obviousness. For example, Lee has expressly stated that orally administration of compositions is unacceptable because of the results that occur to the compound in the liver. According to the ruling in *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984), if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or

motivation to make the proposed modification. This concept is further addressed in the MPEP, wherein section § 2143.01 V – VI states that:

> "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."

Thus, even though the Office seems to be speculating that Lee does not discourage the use of oral route, the specification of Lee expressly states the direct opposite and does discourage a skilled artisan from using an oral route. Thus, the Office has not established a *prima facie* case of obviousness and this rejection must be withdrawn.

2. Claim 1 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and Lee. Applicants insist that this proposed combination does not in any way teach and/or suggest the presently claimed invention.

Initially, it should be noted that the present invention has an effective filing date of June 4, 2001 and the Komarova reference was not published until June 6, 2003. As such, this Komarova reference is not competent prior art and must be removed from this rejection.

The Office has already admitted that the Russo reference does not teach use of PEGylated CT for treating pain, wherein the PEGylation includes PEGylation at $Lys^{11}$ and $Lys^{18}$ residues of CT. Further as stated, above, Lee does not teach or suggest PEGylation at $Lys^{11}$ and $Lys^{18}$ residues of CT and clearly teaches away from oral administration.

As the proposed combination does not teach or suggest each and every element of claim 1, applicants request the withdrawal of this rejection for obviousness.

3. Claim 2 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and in view of Katre and Lee. Applicants insist that the proposed combination suffers from the same shortcomings as that of the obviousness rejection of claim 1.

As previously stated Komarova is not competent prior art and must be removed. Russo does not teach use of PEGylated CT for treating pain, wherein the PEGylation includes PEGylation at $Lys^{11}$ and $Lys^{18}$ residues of CT. Further as stated, above, Lee does not teach or suggest PEGylation at $Lys^{11}$ and $Lys^{18}$ residues of CT and clearly teaches away from oral administration. The addition of Katre does not overcome the shortcomings of the three references because even with all combined disclosures, the presently claimed invention is not disclosed, taught or suggested. As the proposed combination does not teach or suggest each and every element of claim 2, applicants request the withdrawal of this rejection for obviousness.

4. Claim 3 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova, Katre, Crotts and Lee. Applicants insist that the proposed combination suffers from the same shortcomings as that of the obviousness rejections of claims 1 and 2.

As previously stated Komarova is not competent prior art and must be removed. The Office has already admitted that the Russo reference does not teach use of PEGylated CT for treating pain, wherein the PEGylation includes PEGylation at $Lys^{11}$ and $Lys^{18}$ residues of CT. Lee does not teach or suggest PEGylation at $Lys^{11}$ and $Lys^{18}$ residues of CT and clearly teaches away from oral administration. The addition of Katre or Crotts does not overcome the shortcomings of the Komarova, Russo and Lee references because the presently claimed invention is not disclosed, taught or suggested. As the proposed combination does not teach or suggest each and every element of claim 3, applicants request the withdrawal of this rejection for obviousness.

In light of the above discussion and the fact that each and every recited limitation of applicants' claimed invention is not disclosed or suggested in the cited references, applicants submit that the Office has not met its burden of establishing a *prima facie* case of obviousness. Accordingly, applicants respectfully request that all the above rejections of the pending claims, based on obviousness, be withdrawn.

**Multiplicity of Cited References**

Applicants submit that if the Office had a soundly based position on the issue of obviousness, it would not be necessary to rely on so many references. In this regard, the comments of the Board in *Ex Parte*

*Blanc*, 13 USPQ2d 1383 (B.P.A.I. 1989) citing *Ball & Roller Bearing Co. v. F.C. Sanford Mfg. Co.*, 297 F. 163 (2d Cir. 1924) seem particularly pertinent. The Board stated that:

> "It seems necessary to apply to patent litigation from time to time the maxim that one cannot make omelettes of bad eggs--no matter how many are used. One good reference is better than 50 poor ones; and the 50 do not make the one any better."

Other Courts have agreed and have noted that the reliance on a large number of references is persuasive evidence of invention. See, e.g., *Handy v. American Flyer Mfg. Co.*, 6 USPQ 294 (S.D.N.Y. 1930) which stated that:

> "And the citation of many prior references, none showing a solution of the problem presented, is persuasive evidence of invention."

Applicants contend that the use by the Office of a multiplicity of references in an effort to show obviousness is in itself persuasive of the futility of the prior attempts to solve a problem which in hindsight may be very simple but still not obvious.

**Obviousness-Type Double Patenting**

1. Claims 1-2 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 11 and 12 of US Patent No. 7,084,121. In response, a Terminal Disclaimer is being resubmitted (Appendix B) along with a Power of Attorney executed by the assignee of the present invention and a copy of assignment from applicants to the assignee (Appendix C) to overcome the obviousness-type double patenting rejection.

2. Claims 1-3 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38, 62 and 76-80 of US Patent No. 6,770,625, hereinafter Soltero '625. In response, a Terminal Disclaimer (Appendix D) is being resubmitted along with a Power of Attorney executed by the assignee of the present invention and a copy of assignment from applicants to the assignee to overcome the obviousness-type double patenting rejection.

**Fees Payable**

Applicants have included herewith a Terminal Disclaimer with a fee due of $140.00. Still further, applicants have included herewith a Petition for Delayed Priority Claim with a fee due of $1410.00.

All fees are being paid herewith by electronic transfer. If any additional fee is found due for entry of this amendment, the Commissioner is authorized to charge such fee to Deposit Account No. 13-4365 of Moore & Van Allen.

**Conclusion**

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Liu, reconsider the patentability of all pending claims, in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Liu is requested to contact the undersigned attorney at (919) 286-8089 to resolve same.

Respectfully submitted,

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